REMARKS/ARGUMENTS

Claims 1-9, 11-19, 21 and 24-38 are pending in the application. Claims 24-38 were canceled without prejudice to subsequent revival. Claims 1-9, 11-19, 21 are examined on the merits. No claims are allowed. Claim 6 has been amended. Claim 39 has been added and finds support on page 14, paragraph 050. No new matter was introduced by this amendment. The specification has been amended to correct for minor spelling errors. No new matter was introduced by this amendment.

Entry of the amendment, reconsideration of the rejection, and allowance of claims 1-9, 11-19, 21 and 39 are requested.

Applicants gratefully acknowledge the withdrawal of the prior art rejections.

Rejection Under 35 U.S.C. §112

Claim 6 remains rejected under 35 U.S.C. §112, second paragraph, for citing improper Markush language. The claim has been amended to correct for proper Markush language and withdrawal of the rejection is respectfully requested.

Rejection Under 35 U.S.C. §102

Claims 1, 2, 4, 5, 11 and 12 are newly rejected under 35 U.S.C. §102(b) as being allegedly anticipated by Caij *et al.* (*Arch. Virol.* (1989) 105:113-118), cited in the information disclosure statement of February 20, 2003.

The rejection is respectfully traversed.

"Anticipation requires identity of invention. The claimed invention, as described in appropriately construed claims, must be the same as that of the reference in order to anticipate."[1]

The instant invention is directed to a method of producing virus or viral antigen in microcarriers, primarily for the purpose of efficient viral propagation and down stream vaccine production. The claims are drawn to a method of producing virus or viral antigen with cells bound to *microcarriers*, grown to confluence, infected with virus, incubated, harvested, and

[1] *Glaverbel Societe Anonyme v. Northlake Marketing & Supply Inc.*, 45 F.3d 1550, 33 USPQ.2d 1496, 1498 (Fed. Cir. 1995).

purified, wherein the *cell density* of the biomass of the cell culture is *increased* before or after infection. Notably, the instant invention describes a method wherein the cell density is increased in the microcarrier. As described in the specification (page 12, parapgraph [046], last line), this means that the confluent cell culture is concentrated in the microcarrier. This is further explained in Example 2 of the specification (see page 13, paragraph [048]), wherein it is stated that in order to achieve a higher biomass and carrier concentration, the cell culture grown to confluency was concentrated in fermenter B. Example 2 shows that fermenter B contained 200% cell biomass of the original cell culture grown to confluency. The ultimate virus yield per cell was increased compared to the virus yield of cells that are maintained at the same cell density as the original confluent cell culture, resulting in a total antigen concentration of 412.3 (495%) compared to 83.3 (100%) at confluent cell culture conditions (see TABLE 2, page 14). As previously indicated, this was unexpected because a higher cell density in a cell culture microcarrier normally leads to higher physiological stress (*e.g.,* cells slough off the microcarriers) and to a reduction of cell viability and less virus yield.

Caij (Caij *et al.*) teaches a method of producing Togavirus in pig kidney cells in a culture medium supplemented with fetal calf serum, wherein the cells were first grown in Roux flasks (see page 113, last paragraph), subsequently transferred to microcarriers (see page 114, third paragraph), and further propagated via a conventional scale-up system by sub-passaging cells (see page 116, line 2). As such, Caij's method differs substantially from the instant invention. In fact, Caij grows cells in roller bottles and achieves an increase in cell density by moving the cells to microarriers. However, Caij does not teach a method wherein the cell density is increased in the microcarriers. Although, Caij may reduce the volume of growth medium in the cell culture, the author does **not** disclose a method wherein a cell culture grown to confluence is concentrated in the microcarriers. Caij does not even compare microcarrier cultures. Caij only compares a microcarrier culture to a conventional monolayer system (see page 116, paragraph 2).

The instant invention, on the other hand, compares the efficiency of microcarrier cultures (see page 13 and 14, paragraph [048]). Most importantly, the instant claims are drawn to a method for production of virus with the steps of (a) providing a culture of adherent cells

bound to a microcarrier; (b) growing the cell culture to confluence; (c) infecting the cells with a virus; (d) incubating the culture of cells infected with the virus to propagate the virus; and (e) harvesting the produced virus, wherein the cell density of the cell culture grown to confluence is increased in the microcarrier.

The Examiner argues that Caij increases the number of cells and the microcarrier concentration to achieve a maximum yield. But, Caij does not increase the cell density in the microcarriers by concentrating the confluent cell culture, and thus, his method is not identical to Applicants' method. Consequently, Caij does not anticipate the instant invention.

In light of the amendment and arguments presented above, Applicants respectfully request that the rejection of claims 1, 2, 4, 5, 11 and 12 under 35 U.S.C. §102(b), be withdrawn.

Rejection Under 35 U.S.C. §103

Claims 3, 6, 7-9, 13-19 and 21 are newly rejected under 35 U.S.C. §103(a) as being allegedly unpatentable over Caij *et al.* (*Arch. Virol.* (1989) 105:113-118) as applied to claims 1, 2, 4, 5, 11 and 12 above, and further in view of Kessler *et al.* (*Dev. Biol. Stand.* (1999) 98:13-21) and Merten *et al.* (*Dev. Biol. Stand.* (1999) 98:23-37), all of which are cited in the information disclosure statement of February 20, 2003.

The Office Action alleges that one would have had a reasonable expectation of success that influenza virus would have been successfully produced in Caij's method since the method is well known for producing large amounts of viral antigen, as evidenced by Kessler (Kessler *et al.*) and Merten (Merten *et al.*) who use microcarriers to produce their influenza viruses/antigens.

The rejection is respectfully traversed.

Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or

motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art.[2]

As shown above, Caij does not anticipate the instant invention because Caij does not disclose a method wherein cell culture grown to confluence is concentrated in the microcarrier. Thus, Caij's disclosure coupled with the knowledge that influenza virus can be produced in MDCK cells in the absence of serum (see Kessler) and/or the knowledge that the production of influenza virus may be accomplished via serum-free microcarrier cultures using VERO and MDCK cells (see Merten) does not teach the skilled artisan how to produce the claimed invention. There is simply no motivation to combine the references because applying Caij's method to Kessler and/or Merten would not lead to the claimed method.

MPEP 2144.08 states that rebuttal evidence may also include evidence that the claimed invention yields unexpectedly improved properties or properties not present in the prior art[3]; and that office personnel should consider all rebuttal arguments and evidence presented by applicants[4].

The invention provides the unexpected result that the infected cells can be maintained in cell culture for prolonged periods of time, continuously producing viral antigen during that period and thereby greatly increasing the overall viral production efficiency. The specification on page 7, paragraph [027], indicates that the invention obtains a higher virus yield per culture volume due to (i) reduced culture volume and (ii) increased productivity per cell. Caij does not teach an increase in virus yield due to increased productivity per cell.

In light of the amendment and arguments presented above, Applicants respectfully request that the rejection of claims 3, 6, 7-9, 13-19 and 21 under 35 U.S.C. §103(a), be withdrawn.

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[2] *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

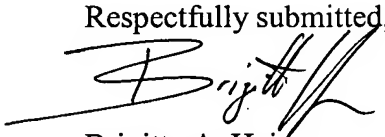
[3] MPEP 2144.08 (II) (B) *Determining Whether Rebuttal Evidence Is Sufficient to Overcome the Prima Facie Case of Obviousness.*

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



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[4] *In re Soni,* 54 F.3d 746, 750, 34 USPQ2d 1684, 1687 (Fed. Cir. 1995) (error not to consider evidence presented in the specification).